

## Synergistic Mortality Caused by *Plasmodium falciparum* during the 1918 Influenza Pandemic

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**Abstract.** At the end of World War I, British medical officers noted that soldiers infected with malaria were more likely to die during the 1918 influenza pandemic than those without malaria. This synergistic mortality appeared to be specific to *Plasmodium falciparum* and has not been generally noted since 1920. A possible explanation is that a malaria-induced procoagulant state enhanced the activation of influenza virus to increase inflammation and subsequent severe clinical outcomes. Falciparum proteins bind and likely inhibit antithrombin 3 and other factors. Pathogens interact in ways that may inform pathophysiology studies of remote epidemics.

*The co-existence of a malarial infection seemed to render the patient extremely susceptible to this post-influenzal pneumonia and to lower his chance of recovery from it almost to vanishing point. (W Angus, Palestine 1919)<sup>1</sup>*

The influenza pandemic of 1918 killed more people than died during World War I.<sup>2</sup> Although influenza pandemics have reappeared intermittently, the extreme mortality of influenza in 1918–1920 has never been well explained, especially its unique concentration in young adults from 20 to 40 years of age.<sup>3</sup> During World War I, British Army soldiers were severely affected by malaria in Palestine (modern Israel/Jordan/Syria), Macedonia (modern Greece), and Mesopotamia (modern Iraq). When the influenza pandemic arrived at the end of the war, severe clinical outcomes were observed nearly everywhere, but some of the highest mortality rates were in soldiers simultaneously infected with falciparum malaria. Although limited by the laboratory resources available in that era, keen clinical observers detected synergistic mortality between falciparum malaria and pandemic influenza in all the three countries and confirmed their findings with postmortem studies.<sup>4–6</sup> That the two pathogens might increase mortality when they simultaneously infected the same person was not surprising, but the independently reported mortality of dually infected soldiers was so great as to raise questions regarding the pathophysiology especially because this effect has not been observed since 1920. Insight may be obtained by constructing plausible scenarios based on modern understanding of infection and inflammation specifically *Plasmodium falciparum*'s effect on the coagulation cascade. An interaction between parasite and viral proteins is hypothesized to be a likely explanation of synergistic mortality during the influenza pandemic of 1918.

The increased mortality of combined influenza and malaria infections was spontaneously noted by the medical officers in 1918 despite the very different military and public health situations in Palestine, Macedonia, and Mesopotamia.<sup>4–6</sup> Postmortem studies in Palestine by Fairley showed 59% of 80 malaria deaths complicated by influenza, in Egypt Manson-Bahr observed 48% of 67 malaria deaths complicated by influenza and in Macedonia out of 100 deaths due to influenza, 83% also had malaria infection.<sup>4–6</sup> The massive number of casualties occurring during the influenza pandemic precluded detailed public health observations from this unanticipated disaster as

all medical units were operating far beyond capacity in addition to having many ill staff members.<sup>7</sup> One demonstration of influenza's synergistic mortality with malaria comes from Macedonia, where in 1918, although the total number of malaria cases decreased, the malaria-attributed mortality increased markedly at the time of the influenza pandemic (the case fatality rate rose, see Figure 1 in reference 8).

The East African campaign had the highest malaria rates in the British Army (599/1000 hospitalized in 1918) during World War I.<sup>9,10</sup> Estimates of the influenza-associated mortality in British and South African troops (56/1000) are much higher than in Indian and African soldiers (15/1000) using Commonwealth War Graves Commission mortality figures with mean troop strength as a denominator.<sup>9,10</sup> This is suggestive that those soldiers more likely to have acute malaria because of lack of immunity also had higher influenza-associated mortality. Equivalent mortality rates from the much less malarious Mesopotamian campaign were 9/1000 in British soldiers and 14/1000 in Indian soldiers.

The mechanism of any synergistic mortality effect between influenza and malaria is unknown, and may simply reflect additive mortality of two serious infectious diseases. Although all soldiers in East Africa were likely to have been infected with malaria at some time during 1918, Indian and African soldiers were more likely than British and South African soldiers to have had a history of previous infections. Attempts to find correlations between influenza mortality and malaria endemicity by district using prospectively collected civilian monthly mortality reports and historical malaria maps from colonial India were unsuccessful indicating either that there were no such relationships or any putative effect could not be distinguished from a background of chronic malaria infection (Katherine Battle and Siddharth Chandra, personal communication).

Modern investigations have suggested possible mechanisms to explain mortality synergy with influenza and malaria. Falciparum malaria commonly causes a procoagulant state although rarely does it progress to clinical bleeding. Although the exact nature of the coagulation disturbance is unclear, it is possibly due to interactions between the parasite histidine-rich protein 2 (HRP2) and elements of the coagulation cascade.<sup>11</sup> HRP2 is a highly positively charged protein excreted in large quantities into the plasma, which binds to negatively charged heparin as well as antithrombin 3. The binding of HRP2 to heparin occurs at nanomolar concentrations and is dependent on zinc ions.<sup>11</sup> Inhibition of the anticoagulant heparin increases tendency toward coagulation just as does the inhibition of antithrombin 3.

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Disturbances of coagulation and fibrinolysis may modify inflammatory reactions to influenza. Plasmin and fibrin are activated serine proteases that increase during influenza possibly activating viral hemagglutinin, and serve as markers of inflammation.<sup>12</sup> It is known that the viral hemagglutinin binds plasminogen which may have a role in its activation and infection of pulmonary cells.<sup>13</sup> A molecular mechanism explaining synergistic mortality during simultaneous malaria and influenza infections therefore may be the cooperative interaction of parasite and host proteins, which may exaggerate pulmonary infection and inflammation.<sup>12</sup> Such inflammation may have increased pulmonary failure or led to ineffective host response to secondary bacterial pneumonias that appear to have been the proximate cause of death of most victims of the 1918 influenza pandemic.<sup>14</sup> Synergistic mortality studies during epidemics involve intrinsically difficult measurements. No similar observations have been reported since 1918 suggesting either that the unique mortality pattern of the 1918 pandemic extended to its interaction with malaria or that subsequently improved therapeutic means such as antibiotics and antimalarial drugs obscured any synergism. Although it has been possible to reconstruct the influenza virus of 1918 from archived pathology specimens, no such materials exist to inform pathogen interaction studies.<sup>3</sup> It may still be possible to use the clinical observations of military medical officers of World War I to better understand the lethality of the 1918 pandemic especially as it relates to dual infections with falciparum malaria.

Received December 8, 2014. Accepted for publication January 12, 2015.

Published online March 23, 2015.

**Acknowledgments:** I thank Katherine Battle of University of Oxford and Siddharth Chandra of Michigan State University for their extensive analysis of public health records from colonial India as well as the librarians and historians who helped locate data.

**Financial support:** G. Dennis Shanks is an employee of the Australian Defence Force and received support for influenza studies from the Armed Forces Health Surveillance Center of the U.S. Department of Defense, Silver Spring, MD.

**Disclaimer:** The opinions expressed are those of the author and do not necessarily reflect those of the Australian Defence Force or the U.S. Department of Defense.

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